Predicting Parameters for Audiological Complications in Pediatric Patients Affected by Meningitis

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Abstract

Background. Meningitis is one of the most common causes of acquired sensorineural hearing loss in childhood.The aim of the study is to identify parameters predicting long-term audiological complications in meningitis.

Methods. Patients under 18 years, admitted to the Bambino Gesù Pediatric Hospital between March 2001 and February 2019 with meningitis were included. Audiological complications regarding treatment and follow-up were investigated: recovery or persistence of the deficit, therapeutic intervention, adaptation to prosthesis.

Results. In the study425 patients were included. Sensorineural hearing loss was observed in 46 patients (11%) with a statistically significant association with pneumococcal etiology ($p < 0.001$) and sleepy state onset ($p = 0.027$). Blood glucose reduction (26.18 mg / dL) ($p = 0.004$), C-Reactive Protein (17.77 mg/dL) ($p=0.01$) and Erythrocyte Sedimentation Rate (106.3 mm/h) ($p=0.04$) increase, were documented. At follow-up, hearing damage was persistent in 19 patients, 7 patients recovered their hearing capacity and 20 patients were lost to follow-up; among patients with permanent hearing damage, treatment was necessary in 16 patients: external hearing aids (6 cases), cochlear implant (10 cases) with incomplete electrode insertion because of cochlear fibrosis and/or ossification development (4 cases).

Conclusion. Thepresence of sleepiness at the onset, blood glucose reduction, inflammation index increase and pneumococcal etiology, have been identified as risk factors for sensorineural hearing damage in meningitis patients.

Background

Meningitis is one of the most common causes of acquired sensorineural hearing loss in childhood.

In children, hearing loss can often be a silent impairment and when it occurs in the first years of life it can seriously compromise the development of language and communication skills (1).

The incidence of post-meningitis hearing impairment ranges from 5–18% (2). Several meta-analysis studies suggest the incidence of permanent hearing damage is around 10–11% (3).

Moreover, a systematic review of the literature about major and minor meningitis sequelae, identified audiological complications as the most frequent sequelae, occurring in 33.9% of cases (4).

The variability of reported incidence of hearing loss depends mainly on differences between hearing testing methods, interpretation of results, and parameters used to define hearing impairment.

Hearing loss can be defined as conductive or sensorineural; depending on severity, it is classified as mild (hearing threshold 20–40 dB), moderate (40–70 dB), severe (70–90 dB), deep (> 90 dB); post-meningitis forms are usually bilateral and deep (5).

The onset of hearing loss is mainly observed in the first days of illness, usually within the first 48 hours, and only exceptionally after the resolution of the infection with a late onset (6, 7).

Hearing impairment after meningitis may be related to several causes: in many cases the underlying mechanism is a suppurative labyrinthitis, spreading from the subarachnoid space through the cochlear aqueduct (8–10); other causes may be a direct damage of the cochlear nerve (11) or a vascular damage, due to septic emboli or thrombotic occlusions of the cochlear artery/vein (12).

Hearing loss pathogenesis includes different stages: a first acute phase, in the first days after onset, followed by a purulent phase, between the first and second week when both non-invasive or surgical treatment is possible and effective. Then it moves to a fibrous stage, between the second and third week from the onset, with granulation tissue and neoangiogenesis processes: the damage can be irreversible, but surgery is still possible. After at least two months from the onset, an ossifying stage occurs, with mineralization and obliteration of the structures of the inner ear; at this stage hearing damage is irreversible and there is no possibility of effective surgical intervention (7, 13, 14).

The aim of the study is to identify a combination of epidemiological, etiological, clinical and laboratory parameters predicting long-term audiological sequelae in patients with meningitis, in order to recognize patients who may require a different therapeutic strategy and/or more detailed clinical and instrumental monitoring.

Methods

Patients under 18 years, admitted to Bambino Gesù Children Hospital (Rome, Italy) for meningitis were included. The study period ranged from 1st March 2001 to 28th February 2019. Children's parent sign an authorization to have their children underwent to the exams related to their disease. The diagnosis of meningitis was obtained by chemical-physical, cultural and biomolecular tests carried out on a cerebral spinal fluid (CSF) sample from lumbar puncture or by the association of clinical evidence of central nervous system (CNS) infection confirmed by positive inflammation indexes on blood samples.

Patients with ventriculo-peritoneal shunt and patients affected by congenital malformation involving skull bones were excluded.

The following data were collected from medical records of hospitalization and follow-up:

- -personal data (sex, age at onset, length of hospitalization),
- -underlying medical conditions,
- -presenting symptoms
- -laboratory tests from blood sample and from CSF: Complete Blood Count (CBC), C-Reactive Protein (CRP), Elevated Sedimental Rate (ESR), CSF glucose and protein levels, CSF White Blood Cells count.

Visual, neurological and hearing impairment information studied both at discharge and during follow-up were documented. Audiological complications were investigated in detail: all patients underwent hearing assessmentaccording to the audiological management protocol currently in use at Bambino Gesù Children's Hospital. It provides for the execution of first level oto-functional tests (TEOAE or AEP or pure tone audiometry) at the end of the isolation period (about 7–10 days from the onset); in case of normal results, tests were repeated at discharge and, with normal findings again, patients stopped the follow-up program.

If unilateral sensorineural hearing loss was found, the follow-up continued with six-monthly or annual checks; if bilateral sensorineural hearing loss was found, high-resolution temporal computed tomography (CT) scans and magnetic resonance imaging (MRI) with gadolinium for the study of the inner ear and 3D reconstructions of the membranous labyrinth, was performed urgently in order to identify signs of labyrinthine fibrosis or ossification. These tests have a sensitivity of 94% and specificity of 88% (5, 15). If ossification was detected, urgent bilateral simultaneous cochlear implantationwas indicated in cases with severe or profound sensoneural hearing loss. Otherwise, the follow-up continued by repeating imaging and audiological evaluation after 15 days; without any evidences of improvement, the patient received appropriate treatment (cochlear implantation or hearing aid fitting) within 6 weeks of onset according to the degree of hearing impairment.

Treatment options for sensorineural hearing loss included hearing aids for mild, moderate and severe hearing loss, or cochlear implantation for profound sensorineural hearing loss. According to Italian guidelines, cochlear implantation surgery, is recommended in children from 1 year age with severe or profound bilateral deafness (hearing threshold > 75 dB HL) evidenced by both subjective and objective audiometric techniques and in cases of no improvement of hearing and communication skills, after 3–6 months of treatment with hearing aids and speech therapy (5, 16). However, in profound sensorineural hearing loss cases due to meningitis bilateral simultaneous cochlear implantation surgery is mandatory even under 12 months.(5, 15).

The study population was characterized using descriptive statistics: mean value ± SD for continuous variables and proportions for categorical variables. The reported data were compared with Mann-Whitney test (for continuous variables with non-normal distribution) and Chi-Square test for categorical variables; a value of $p < 0,05$ was considered statistically significant.

Results

General epidemiological, etiological and clinical data

Four-hundred twenty-five patients entered the study, 261 male (M) and 164 females (F) (M: F ratio of 1.6: 1). The mean age was 3.96 years (range from 0.01 to 17.68). The highest frequency of disease cases was in infants younger than 1 year old (171 patients), while 124 patients were between 1 and 5 years old,

78 were between 5 and 10 years old, 52 were between 10 and 18 years old. The mean time of hospitalization was 25 days.

The presence of pre-existing pathological conditions that could predispose to the development of serious infections has been evaluated: 3 patients with severe heart disease, 5 cases of immunoglobulin deficiency, a case of hypocomplementemia, a patient with autoimmune lymphoproliferative disease, 2 patients with brain neoplasms, 4 patients with non-derivative hydrocephalus, 2 patients with Arnold Chiari type I syndrome, 3 cases of prematurity.

Most cases of meningitis had bacterial etiology (218 cases), in 49 cases a viral etiology was found, while in 158 cases it was not possible to identify the causative pathogen. The culture tests and molecular tests performed on CSF and blood, identified Neisseria Meningitidis (NM) as the first causative pathogen by frequency, responsible for 16.47% (70 subjects), followed by Streptococcus Pneumoniae (SP), isolated in 14.35% of the patients (61 cases). Figure 1 shows the most observed pathogens and the differences related to age.

The most common onset symptom observed was fever, in 85.65% of patients (n = 364), followed by vomiting and nuchal rigidity, respectively found in 31.76% (n = 135) and 20.76% (n = 88) of cases, while 20% of patients presented in a sleepy state at onset.

The lumbar puncture liquor examination, performed in 407 patients, showed a mean glucose concentration of 37.78 mg / dl, a mean protein value of 180.27 mg / dl and a mean white blood cell count of 1940.13 / mmc.

Blood parameters mean value have been evaluated: Hemoglobin 11.85 g / dl, white blood cell count 15250 / mmc (with 67.9% of neutrophils and 35.8% of lymphocytes), total platelets 342.862/mmc, CRP of 12.37 mg / dL (normal values 0.5 mg / dL) and ESR of 74.98 mm / h (normal values 0–13 mm / h).

General Complications

A percentage of 1.4% of patients examined died during hospitalization (6/425).

The onset of neurological, visual and audiological sequelae has been studied in the 419 surviving patients, finding a total of 119 complicated cases (28%), 90 characterized by a single complication and 29 by the association of two or more sequelae. Neurological complications were the most frequent observed (83 cases, 19%), followed by auditory complications (46 cases, 11%) and visual complications (27 cases, 6%). In a percentage of 11% (46 patients), the disease was complicated by the onset of hearing impairment, clinically evident in 44 patients and detected or confirmed by audiometric examination in all the 46 patients.

Audiometry has identified 9 cases of profound deafness, unilateral in 4 cases and bilateral in 5 cases; in 36 cases the hearing impairment has been classified as sensorineural hearing loss, bilateral in 21

subjects and unilateral in 15 subjects; only one patient reported mixed damage with left and right hearing loss.

In addition, hearingimpairment was associated with visual impairment in 5 cases and with neurological sequelae in 16 cases.

Considering patients with hearing impairment, a gender prevalence was observed (M: F ratio of 2.83: 1, 34 males and 12 females); mean age was 4.37 years (range 0.19–16.64); most of our sample was aged 1 to 5 years (17 cases). The mean duration of hospitalization was 26.37 days.

Considering the etiology, most cases were related to SP (41%, 19 cases), while NM infection was detected in a percentage of 24% (11 cases).

Clinically, the onset of meningitis was characterized by fever in a percentage of 91%, associated with the typical symptoms of acute meningitis: vomiting (15 cases, 32.61%), neck stiffness (11 cases, 23.91%) headache (10 cases, 21.74%), sleepy state (15 cases, 32.61%).

Lumbar puncture showed a higher level of white blood cells in the CSF (2846 / mmc) and a marked reduction in glucose concentration (26.18 mg / dl) while the protein concentration was increased similarly to the total sample (181.5 mg / dl); finally, a significant increase in CRP (17.77 mg/dl) and ESR (106.3 mm/h) and a reduction in the platelet count (280.337 PLT / mmc) were detected.

At the follow-up evaluation, 7 patients had an improvement of the auditory function; in 19 patients the audiological evaluation showed persistence of the deficit; finally, data on follow-up are not available for 20 patients.

Patients with audiological impairment, continued the follow-up evaluation with the execution of CT and MRI to highlight signs of ossification of the inner ear. In particular, treatment was required in 16 patients: hearing aids in 6 cases, cochlear implant in 10 cases.

Unfortunately, in 4 out of 10 cases, in which audiological screening was delayed, cochlear fibrosis and / or ossification were observed, with a definitive hearing damage.

Among patients undergoing surgical treatment there was a clear prevalence of pneumococcal etiology, responsible for 7 of the 10 cases of meningitis complicated by severe-profound hearing loss (70%).

Comparing patients with audiological complications and those uncomplicated we observed a greater frequency of audiological complications in male patients with a ratio of 2.83: 1 in complicated cases and 1.49: 1 in the uncomplicated ones ($p = 0.065$).

Comparing the mean age at diagnosis – 4.37 and 3.97 years respectively - the Mann-Whitney test shows no significant difference between the group of patients with hearing loss and the group without hearing impairment ($p = 0.26$).

In cases with hearing damage, a duration of hospitalization of 26.37 days was shown, compared to the remaining population (24.9 days), which was significant for p = 0.0112.

Analysing the etiology of the two groups, a significant association between hearing impairment and pneumococcal etiology was observed (41% vs 10.79% cases of uncomplicated patients) (p < 0.001). Meningococcal etiology showed a higher prevalence in the group of patients with sensorineural hearing loss compared to the rest of the sample (24% and 15.3% respectively), however the difference was not significant (p = 0.1476).

As for laboratory, a reduced glucose in CSF was detected in patients with hearing impairment (26.18 mg / dL compared to 39.3 mg / dL of patients without hearing impairment) (p = 0.004). In complicated patients, there was also a greater increase in protein CSF levels (181.5 mg / dL in hearing impaired patients and 180.12 mg / dL in uncomplicated ones) and a higher number of white blood cells in the CSF (2486 / mmc and 1830 / mmc respectively); these values were not statistically significant (p = 0.1090 and p = 1.000).

We demonstrated a statistically significant increase of inflammatory laboratory parameters in patients with hearing impairment: higher CRP (17.77 mg/dL) (p = 0.01) and ESR (106.3 mm/h) (p = 0.04);a lower average platelet count was detected in hearing impaired patients compared to the rest of the sample (280.337 and 350.714 respectively), with a tendency to significance with a p-value of 0.0501.

Table 1 and Table 2 summarize the results.

Table 1
Organism responsible for hearing loss in meningitis pediatric patients

Organism	Hearing loss (n, %)	No hearing loss (n, %)	p
HaemophilusInfluenzae	2 (4)	12 (3.16)	0.750
Streptococcus Pneumoniae	19 (41)	41 (10.79)	< 0.001 [b]
Neisseria Meningitidis	11 (24)	59 (15.35)	0.147
B-Streptococci	1 (2)	33 (8.68)	0.123
Mycobacterium Tuberculosis	1 (2)	22 (5.79)	0.304
Herpes Simplex virustype 1	1 (2)	7 (1.84)	0.877
Enterovirus	1 (2)	28 (7.37)	0.185

Table 2
Demographic, clinical, laboratory parameters and treatment

Variable	Hearing loss	No hearing loss	p
Duration of hospital stay (days), mean ± SD, median	26,37 ± 14,03; 49,11	24,90 ± 28,322; 17	0,012 [a]
Fever, n (%)	42 (91,30)	322 (84,74)	0,246
Seizures, n (%)	5 (10,87)	53 (13,95)	0,561
Lethargy, n (%)	15 (32,61)	71 (18,68)	0,027 [b]
Neck stiffness, n (%)	11 (23,91)	78 (20,53)	0,599
Serum WBC count, x 10^3 ml, mean ± SD, median	19523 ± 40282; 32363	14738 ± 17053; 11490	0,152
Platelet cell count, cells /mm^3, mean ± SD, median	280337 ± 167675; 271000	350714 ± 188821; 307000	0,051 [a]
CSF WBC count, cells/ mm^3, mean ± SD, median	2846 ± 5518,58; 440	1830,3 ± 4373,13; 300	1,001
CSF protein, mean ± SD, median	181,5 ± 150,08; 137,2	180,12 ± 279,4; 96	0,109
CSF glucose, mean ± SD, median	26,18 ± 19,99; 28	39,3 ± 28,31; 37	0,004 [a]
CRP (mg/dl), mean ± SD, median	17,77 ± 12,35; 17,9	11,76 ± 18,44; 6,49	0,001 [a]
ESR (mm/h) mean ± SD, median	106,3 ± 33,75; 107	70,5 ± 43,604; 60	0,004 [a]

Legend: SD = standard deviation; n = number; WBC = white blood cells; CSF = cerebral spinal fluid; CRP = C-Reactive Protein; ESR = erythrocyte sedimental rate.

Finally, no statistical significance was detected considering corticosteroid treatment and audiological impairment. In particular, Table 3 shows the relation between corticosteroid treatment, pathogens involved and audiological impairment.

Table 3
Corticosteroid therapy and audiological complications in bacterial meningitis

	Hearing loss (n, %)			No hearing loss (n, %)			
Pathogen	CT	NT	NA	CT	NT	NA	p
StreptococcusPneumoniae	12 (19)	2 (3)	6 (9)	24 (39)	13 (21)	4 (6)	0.144[a]
NeisseriaMeningitidis	7 (10)	0 (0)	4 (5)	43 (61)	9 (12)	7 (10)	0.231[a]
HaemophilusInfluenzae B	1 (7)	0 (0)	1 (7)	8 (57)	2 (14)	2 (14)	0.621[a]

Legend: CT = Corticosteroid therapy; NT = No corticosteroid therapy; NA = missing data; a = chi-square test; b = Mann Whitmann test

Discussion

Patients who experienced bacterial meningitis report numerous sequelae including neurological, audiological and cognitive ones (3) (17). Approximately, a percentage of 25% of survivors of meningitis in the United States have moderate or severe sequelae (17) (18).

In particular, sensorineural hearing impairment is one of the most frequent complications described (3) (12) (19). Sensorineural hearing loss following meningitis is a serious complication, and is permanent approximately in a percentage of 10% of survivors of bacterial meningitis while other children experience a transient hearing loss (3). In the present study, we observed a sensorineural hearing loss prevalence following meningitis of 11%. This was consistent with other reports (3) (4).

According to several studies, the main factors associated with poor prognosis and neurological or audiological sequelae are: S. Pneumoniae (SP) infection, lower levels of glucose in Cerebral Spinal Fluid (CSF) and, frequent but less significant, higher levels of proteins in CSF (12, 20, 21); particularly, in pneumococcal meningitis the onset of hearing loss was observed in 21 to 50% of cases (22, 23). Also, intracranial hypertension, demonstrated on CT, neck stiffness among presenting symptoms, prolonged hospitalization and male sex, seem to be associated to audiological sequelae (12) (21) (24) (25).

Conversely with most prior Studies, our research did not show any connection between hearing loss to male gender with a ratio of 2.83: 1 in complicated cases and 1.49: 1 in the uncomplicated ones (p = 0.065) (14). Otherwise, our study is congruous with Karanja et al. findings (24). Moreover, a longer hospitalisation time has been documented in complicated patients.

Considering predictor factors of audiological impairment, etiological, clinical and laboratoristic parameters have been discussed.

In particular, a higher incidence of hearing impairment was detected in SP infections (31.4% of the total cases of pneumococcal meningitis). Moreover, SP has become the leading cause of meningitis in children, after Haemophilus influenzae B (Hib) vaccine introduction (27) (28).

A statistical significance was observed between clinical lethargy onset and audiological sequelae: this means that a severe neurological clinical onset and an altered mental status should be considered as a predictor factor of audiological complications. To our knowledge this is the first study that highlights a statistically significant difference between patients with and without sleepy state onset concerning the development of audiological sequelae.

Lower values of CSF glucose have been detected in patients with audiological impairment. This was statistically significant. This correlates to greater number of organisms in the CSF and to severity of the infection (23).

Higher values of inflammatory parameters (CRP and ESR) have been documented in complicated patients. Our findings are similar to those reported in the literature (27).

The role of dexamethasone in pediatric meningitis is still controversial. Some Researchers found that an early use of corticosteroids reduces the incidence of hearing loss in Hib meningitis and in animal models, but also labyrinthitisossificans occurrence that is a major cause of incomplete ochlear implant insertion, with subsequent poor functional outcomes. (29) (30) (31) Our results evaluated dexamethasone role in audiological complication development: it did not appear to decrease deafness incidence, consistent with previous studies (32). Moreover, we separated out therapy given according to pathogens and it did not appear to reduce hearing loss. Whereas the literature showed a protective role of glucocorticoid treatment for hearing impairment in case of Hib infection, our study didn’t show any statistically significant differences (Table 3) (32) (23). Nevertheless, corticosteroid treatment in children should be individualised because a clear survival benefit has not yet been demonstrated.

One potential limit of our study is the poor patients’ adherence to follow-up evaluation.

Future perspectivescould be the study of cortisone treatment role in terms of time of starting and time of duration in order to create a predictive algorithm for audiological impairment.

Further studies are necessary to enforce our results.

Conclusion

In conclusion, our study highlights factors predicting hearing loss development in meningitis pediatric patients: SP infection, lethargy onset, higher values of CRP and ESR, lower CSF glucose levels and total platelet count. However, independent of the presence of these factors, clinicians should always apply a

prompt audiological screening in order to earlier detect any hearing impairment, make the right treatment and improve outcomes.

Abbreviations

CSF
Cerebral Spinal Fluid
CNS
Ventral Nervous System
CBC
Complete Blood Count
CRP
C-Reactive Protein
ESR
Elevated Sedimental Rate
CT
computed tomography
MRI
magnetic resonance imaging
M
male
F
female
NM
Neisseria Meningitidis
SP
Streptococcus Pneumoniae
Hib
Haemophilus Influentiae B

Declarations

- Ethics approval and consent to participate: ethic approval was not required as the exams were part of their diagnostic programme and the data were properly anonymised. At hospital admission parents signed an authorization to get their children underwent exams related to the diagnostic and therapeutic programme. (https://www.bio.cam.ac.uk/psyres/approval)
- Consent for publication: not required
- Competing interests: no
- Funding: no

- Authors' contributions EB planned the study, GS and CM collected the data, PM and AS performed audiological investigations, MS and AV revised the literature. All authors have read and approved the manuscript.
- Acknowledgement: no
- Availability of data: at Bozzola's office

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Figures

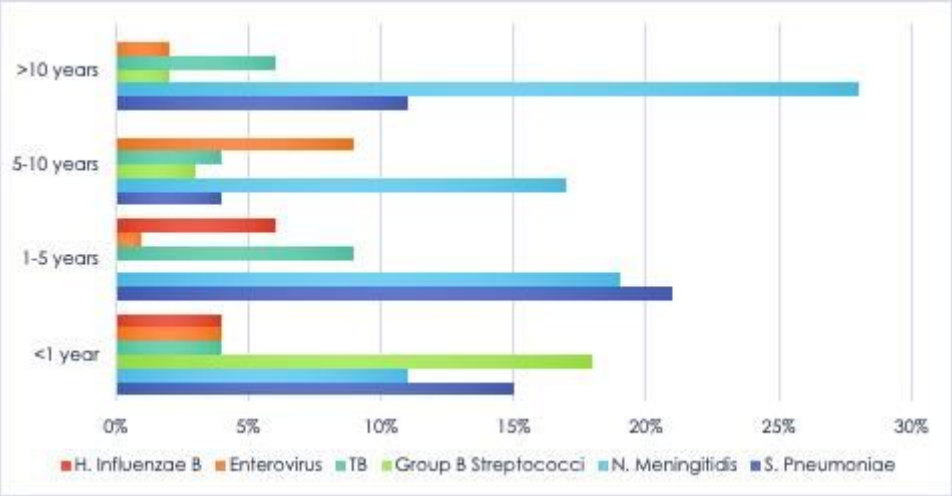

Figure 1

Pathogens detected in meningitis patients by age group